ACT NOW OR LATER? ECONOMICS OF MALARIA RESISTANCE

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Abstract.   In the past, malaria control efforts in sub-Saharan Africa have relied on a combination of vector control with effective treatment using chloroquine. With increasing resistance to chloroquine, attention has now turned to alternative treatment strategies to replace this failing drug. Some countries have already changed their official first-line treatment to sulfadoxine-pyrimethamine, while others are contemplating a switch to artemisinin-based combination treatments (ACTs). Although there are strong theoretical arguments in favor of switching to ACTs, the validity of these arguments in the face of financial constraints has not been previously analyzed. In this report, we use a bioeconomic model of malaria transmission and evolution of drug resistance to examine questions of optimal treatment strategy and coverage when drug resistance places an additional constraint on choices available to the policymaker.

INTRODUCTION

Parasite resistance to chloroquine (CQ) has increased steadily in recent years in many malaria-endemic countries in sub-Saharan Africa, with consequent increases in malaria morbidity and mortality.[1] The imminent loss of this important drug in the fight against malaria has hampered malaria control efforts and placed greater responsibility on policymakers to rapidly change their guidelines on antimalarial treatments, keeping in mind the possibility that alternatives to CQ also could be rendered obsolete by drug resistance. Given the limitations on financial resources in most malaria-endemic countries, there has been considerable difficulty in deciding on an alternative treatment that is both affordable as well as sound from a long-term perspective. Artemisinin-based combination treatments (ACTs) hold considerable promise of both increased efficacy and retardation in the rate of development of parasite resistance. Although the theoretical basis underlying the epidemiological advantages of artemisinin-containing combinations in the treatment of malaria has been studied,[2–5] little attention has been paid to the economic desirability of using ACTs. The focus of this report is on the economic evaluation of alternatives to the current CQ guidelines, and the implications for the allocation of scarce financial resources for malaria treatment, when future resistance is a consideration.

In response to growing resistance to CQ, many countries have considered changing their official guidelines for first-line treatment to either sulfadoxine-pyrimethamine (SP) or ACTs. Sulfadoxine-pyrimethamine offers distinct advantages over ACTs in that it costs roughly one-tenth that of ACTs per treatment dose, is administered as a single treatment, and is approved for use in children and pregnant women.* An important drawback with switching to SP, however, is that resistance to the drug is expected to increase with widespread use[†] and may leave policymakers with a similar situation of growing malaria morbidity and mortality a few years from now.[6] An alternative strategy would be to switch to ACTs

immediately. The ACTs offer the advantage of delaying resistance for a much longer time period than SP while offering faster cure rates. However, there is some concern about whether ACTs would actually work to delay resistance in sub-Saharan Africa, where there is poor adherence to treatments and underdosing, among other concerns.[7] Furthermore, there is uncertainty about the benefits of ACTs because of the potential for monotherapy, which is the use of only one of the drugs rather than the combination prescribed for therapy.

In this report, we develop a mathematical, bioeconomic model of malaria transmission, immunity, and drug resistance. The model is then applied to addressing two specific questions. First, we compare the economic consequences of two strategies, the first of which involves replacing CQ with ACTs, and the second of which involves replacing CQ with SP and waiting for resistance to develop before introducing ACTs. The second question addressed in this report pertains to the optimal level of coverage using ACTs. Here one is faced with the constraint that while increasing access to an effective antimalarial in any given region or location both lowers morbidity and saves lives, it involves higher costs and an increasing likelihood that resistance will develop to the drug being used.[‡] Furthermore, policymakers may have to decide whether to devote all their resources to increasing treatment coverage in a few regions or to distribute these resources over a larger number of regions.

MATHEMATICAL MODEL

The use of antimalarials involves costs and benefits that occur at different points in time. On the one hand, using effective antimalarials in the present benefits society by lowering the current economic burden of malaria morbidity. On the other hand, expanding the use of antimalarials, while increasing the cost of treatments, potentially increases the likelihood that resistance will evolve, which in turn could lead to greater morbidity in the future. Converting present and future morbidity and deaths into economic metrics permits a

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* There is substantial disagreement over the cost of ACTs. Current estimates vary between $1.00 per adult dose (Médecins Sans Frontières) and $2.50 for artemether-lumafantrine at the price negotiated by the World Health Organization for developing countries. It is likely that with widespread adoption of new ACTs, the price will decrease significantly and the lower estimate of $1.00 would be a reasonable approximation of the long-term marginal cost of these treatments. The current price for SP is roughly $0.12 per dose.
[†] This situation has already arisen in Southeast Asia.

[‡] Although the use of ACTs is less likely to induce resistance than the use of drugs in monotherapy, the probability of increased resistance to ACTs is greater for higher levels of treatment coverage. However, if increasing ACT coverage implies less use of the partner drug in monotherapy, then this could lower the likelihood of resistance to ACTs.

consistent comparison of different strategies for antimalarial use over the policymaker's planning horizon.

The policymaker's objective is to inter-temporally minimize the sum of discounted present value of the costs of infection and the costs of treatment. This objective is constrained by the biology of the disease as reflected by the dynamics of malaria transmission and the evolution of drug resistance. Disease dynamics are modeled using a compartmental model where individuals move between healthy (susceptible), infected, and immune classes. Although factors such as age structure, degree of parasitemia, latency, and genetic variability play an important role in malaria dynamics, the model presented is abstracted from these secondary considerations to focus sharply on the role of treatment in malaria transmission and the evolution of resistance and immunity. Malaria transmission is assumed to be year-round and stable. A constant population size is assumed with no net migration or change in age structure. Superinfections are ruled out, although this may make a quantitative difference in terms of increasing infection rates.[8]

Biology. We follow the basic mathematical model of malaria described by Koella[9] and earlier papers[10,11] modified to incorporate the evolution of resistance (see Figure 1 for a schematic).[§] As in previous literature in this area, we assume that the mosquito dynamics operate on a much faster timescale than the human dynamics, so that the mosquito population can be considered to be at equilibrium with respect to changes in the human population, and its dynamics can be collapsed into the inoculation rate.[9]

Resistance arises in this model in the following way. Initially, there is a small proportion of infected individuals who carry a resistant strain. This initial frequency of resistance is believed to be in the order of magnitude of 10^{-12} in the case of ACTs and 10^{-3} for treatment with SP. Over time, treatment selection pressure leads to a greater prevalence of infected individuals who carry the resistant strain relative to those that carry a sensitive strain. However, resistant strains face an evolutionary disadvantage in the absence of antimalarials. This notion of the fitness cost of resistance is manifested in a higher patient recovery rate from resistant infections, as described in the model below.

The inoculation coefficients are given by

$$h_w = ma^2 b_1 b_2 e^{-\mu T} \frac{y_w}{\mu + ab_1 y}$$

and

$$h_r = ma^2 b_1 b_2 e^{-\mu T} \frac{y_r}{\mu + ab_1 y}$$

(see Appendix 1 for derivation) for wild-type and resistant strains, respectively, where a is the biting rate (number of bites per female mosquito per night), b_1 is the infectiousness of humans to mosquitoes, b_2 is the susceptibility of mosquitoes to humans, m is the mosquito density (number of mosquitoes per human), τ is the incubation period of parasites in the mosquito, and μ is the mortality of mosquitoes. y denotes
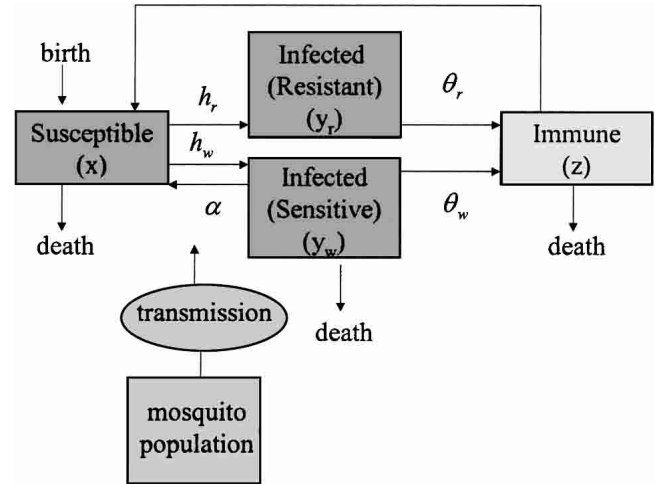

FIGURE 1. Model of disease transmission and treatment.

the proportion of infected individuals in the human population (see Equations 1–4), y_w is the fraction of infected patients with a susceptible strain, and y_r carry a resistant strain ($y_w + y_r = y$). Let the proportions of susceptible individuals and immune individuals be denoted by x and z so that $x + y_w + y_r + z = 1$. The differential equations that describe changes in the classes of susceptible individuals, infected individuals (wild-type or sensitive strain), infected individuals (resistant strain), and immune individuals are

$$\dot{x} = \delta - \delta x - x(h_w + h_r) + \gamma z + f\alpha y_w \tag{1}$$

$$\dot{y}_w = h_w x - (\theta_w + \delta) y_w - f y_w \tag{2}$$

$$\dot{y}_r = h_r x - (\theta_r + \delta) y_r \tag{3}$$

$$\dot{z} = \theta_w y_w + \theta_r y_r - \gamma\ z - \delta z \tag{4}$$

Susceptible (or healthy) individuals become infected with a sensitive parasite at rate h_w, the inoculation rate for sensitive individuals, and with a resistant parasite at rate h_r, defined earlier.[¶#] Individuals with a wild-type strain recover at rate θ_w to enter the immune class, while individuals with a resistant strain recover at rate θ_r. The spontaneous rate of recovery from the resistant infection is assumed to be greater than that for sensitive infections; thus, $\theta_r \geq \theta_w$. The difference between these rates represents the treatment fitness cost of resistance.[‖] Immune individuals become susceptible again at rate γ. The period for latency of infection in humans is assumed to be zero. α represents the rate of recovery of patients infected with a wild-type infection who receive treatment. The inverse of this parameter, therefore, represents the mean duration of illness for a treated individual with a wild-type infection. δ is the population death (and birth) rate and is unrelated to dis-

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§ Since this paper was completed, a new report has been published by Koella and Antia[12] that incorporates resistance into a model of malaria transmission. Their model differs only in minor respects from the one developed in this paper.

¶ Interventions such as impregnated bed net use will likely reduce this transmission coefficient. Although the use of ACTs is expected to reduce gametocyte carriage and thus parasite transmissions, we shall assume that ACTs reduce transmission primarily by curing patients more rapidly.

Some of the mathematical epidemiology literature on malaria resistance focuses on the relative importance of transmission rates on evolution of drug resistance.[13,14]

‖ For a discussion of the fitness cost of resistance, see the report by Koella.[15]

ease status. Transmission fitness cost of resistance is assumed to be negligible.[+] Births equal deaths, so the population size remains unchanged.

f is the fraction of the infected population that receives treatment. Infected individuals who are treated successfully (because they carry a sensitive parasite) return to the susceptible state. There is some evidence that the benefit of effective treatment is accompanied by a loss of immunity.[17,18] Treatment, therefore, retards expansion of the immune class. The use of ACTs or some similar effective treatment strategy does not alter transmission intensity in this model, but reduces the number of parasites in circulation by reducing the duration of illness.

In any period, the fraction of malarial parasites that are resistant to the drug, r, is defined as

$$r = \frac{y_r}{y_r + y_w} \tag{5}$$

It is customary to describe the basic reproductive number as the number of secondary cases of malaria arising from a single case in an otherwise uninfected population.[19] In our model, the reproductive number depends on whether this case is of a wild-type strain or a resistance strain. The reproductive number of susceptible and resistant parasites is given by

$$R_w = \frac{ma^2 b_1 b_2 e^{-\mu T}}{(\theta_w + \delta + f\alpha)\,\mu} \text{ and } R_r = \frac{ma^2 b_1 b_2 e^{-\mu T}}{(\theta_r + \delta)\mu}$$

respectively (see Appendix 2 for derivation).

The ratio of reproductive numbers is

$$\frac{R_r}{R_w} = \frac{\theta_w + \delta + f\alpha}{\theta_r + \delta}.$$

Increasing treatment coverage increases this ratio. At $f = 0.5$, this ratio is equal to 3 for the baseline parameter values used in our model. In other words, if 50% of the infected population were to receive treatment, a resistant strain introduced in a population comprised entirely of susceptible individuals is three times as likely to generate a secondary infection as a wild-type strain. The critical coverage at which the increase in resistance due to selection pressure placed on sensitive strains is exactly equal to the decrease in resistance because of the fitness cost associated with resistance is

$$f_c = \frac{\theta_r - \theta_w}{\alpha},$$

which is roughly 0.12 for the parameter values used in our model (see Appendix 3 for derivation). At this steady state level of coverage, the level of resistance to the drug remains unchanged. Higher levels of coverage are associated with increasing resistance, while lower levels of coverage are associated with decreasing resistance.

Economics. A number of studies have examined the direct and indirect costs of an episode of malaria.[20–24] However, these costs tend to be highly context- and location-specific,

with limited applicability to other settings.[25] A range of cost estimates for morbidity and treatment are drawn from the existing literature to allow a sensitivity analysis based on variations in the cost parameters.

Estimates of lost work time range from one to five days per episode. In general, indirect costs associated with lost productive labor time account for a relatively large fraction of the overall costs of malaria. For instance, a study that surveyed 1,614 households in rural Ghana found that the average direct cost of treating malaria, which included the cost of drugs, consultation, laboratory service, and transportation, constituted roughly 20% of the cost of treatment.[26] Indirect costs that measured the opportunity cost of travel, time, waiting, and loss of productive time made up the remaining 80%.[26] Another study that compared malaria-related costs in four sites in Africa (in Rwanda, Burkina Faso, Chad, and Congo) found that, on average, a case of malaria cost \$1.83 (1987 dollars) in direct costs (treatment expenditure and control) and \$9.84 in indirect costs (morbidity, mortality, and economic losses).[27] In all sites, the indirect costs were much higher than the direct costs and typically accounted for roughly 90% of total costs (excluding quality-of-life costs). These studies indicate that the cost of drug treatment may only be a small percentage of the overall costs of treating malaria.

For the purpose of our simulations, we assume a morbidity cost of \$1.50 per infected patient per day for the baseline analysis, based on the above cost estimates and average duration of illness. In the base case, the cost of a dose of SP was assumed to be \$0.12 and the cost of ACTs was assumed to be \$1.00.[˜] Non-drug treatment costs were assumed to be zero in the baseline analysis. Higher non-drug treatment costs were likely to make differences in the cost of the drug itself less critical in the choice of strategy.[≈] Including the cost of treatment favors the strategy of introducing ACTs immediately since the cost of the drug may not add substantially in percentage terms to the costs associated with malaria. Finally, all costs were discounted at a constant, annual rate of 3%.

Analysis. The initial conditions for the model were such that the disease was in steady state and there was no drug in circulation. A proportion of newly infected cases are treated immediately. Present discounted cost of treatment and infection for different levels of coverage were computed and compared for two treatment strategies, as described below.

$$\text{Discounted Cost} = \int_0^T (C_y + C_T fy)\, e^{-\rho t} dt \tag{6}$$

[+] It is possible that resistant parasites are less likely to be transmitted from humans to mosquitoes and back and this places them at an evolutionary disadvantage with respect to sensitive parasites. It is also possible that resistant parasites are more likely to be transmitted, which gives them a transmission fitness advantage.[16]

[˜] In a recent paper, Snow and others[28] report a \$1.20 cost for an adult dose of artesunate plus SP (sulfadoxine, 25 mg/kg of body weight over a one-day period; pyrimethamine, 12.5 mg/kg of body weight over a one-day period; artesunate, 4 mg/kg of body weight over a three-day period); \$1.30 for an adult dose of artesunate plus amodiaquine (amodiaquine, 25 mg/kg of body weight over a three-day period; artesunate, 4 mg/kg of body weight over a three-day period); and \$2.40 for an adult dose of Coartem® (lumefantrine, 48 mg/kg of body weight over a three-day period; artemether, 8 mg/kg of body weight over a three-day period).

[≈] If non-drug treatment costs were for example \$4, then the cost of ACT treatment is only roughly 20% higher than that of SP treatment. With zero non-drug treatment costs, the relative cost of ACT treatment is higher. One reason for including only the drug costs was to examine the problem from the perspective of a Ministry of Health that is concerned about the impact on its drug budget of different treatment strategies.

where T is the time horizon, ρ is the discount rate, C_y is the cost of illness and C_T is the unit cost of treatment. In strategy A, ACTs were introduced immediately and resistance was allowed to evolve as an increasing function of treatment coverage. In strategy B, SP was introduced at time 0 and resistance was allowed to evolve to 20%, at which point the treatment was switched to ACTs. The resistance switch point was selected arbitrarily and one could well make a case for it being higher or lower. The switch point was varied to 60% in the sensitivity analysis.

Computations were made for a base population of one million. To focus on the cost of ACTs and the optimal levels of coverage based on treatment and infection costs, we made the simplifying assumption that those who do not receive ACTs take CQ or some other drug that does not compromise the long-term efficacy of the combination treatment. If this assumption were to be relaxed, we find that we may be worse off with very low levels of ACTs coverage (relative to coverage with monotherapy with either drug in combination) than with no ACT use at all. Furthermore, the success of ACTs would depend largely on reducing use of the artemisinin derivative's partner drug in monotherapy. Malaria-specific mortality was assumed to be zero, although introducing an appropriate case-fatality rate did not alter any of the results qualitatively.

Model parameters are summarized in Table 1 and justification is provided in Appendix 4. In addition, we have conducted extensive sensitivity analyses around these point estimates, some of which are described in the following section.

RESULTS

Since the parameter values used in the simulations were intended to broadly represent the situation in sub-Saharan Africa and are not precisely applicable to any single context, it is probably more useful to focus on the qualitative results and orders of magnitude indicated rather than on the numbers themselves. Figure 2 plots the infection rates and resistance for three levels of coverage (20%, 40%, and 60%) over three time horizons, 5, 10, and 20 years, to represent the short, medium, and long term for different runs of strategy A. Infection rates initially decrease in response to the introduction of the effective drug to replace CQ. However, the decrease in infection rates attributable to the effective drug is partly offset by increasing levels of infection because of decreasing

immunity. Infection levels further increase in response to increasing resistance. The increase in infection levels is most rapid for higher rates of treatment coverage, which also achieve greater reductions in infection levels in the short term because more patients are being treated. In the longer term, infection levels decrease with the increase in immunity to the parasite.

The increase of parasite resistance follows the familiar logistic function. The third plot describes the present discounted cost of treatment and infection for three different levels of coverage with an effective treatment such as combination treatment. Higher levels of treatment coverage shifted the cumulative discounted cost curve downwards.

Figure 3 plots the present discounted value of treatment and infection costs for strategy A under the base case parameter values over three time horizons, 5, 10, and 20 years, to represent the short, medium, and long term. Costs of infection decreased for increasing levels of coverage, but at a decreasing rate. Treatment costs increased linearly with treatment coverage. Even at high levels of coverage, treatment costs represent only a small proportion (roughly 5%) of the economic costs associated with malaria morbidity.

The same graph is repeated for strategy B, where SP was introduced to replace CQ, in Figure 4. Here too the costs of malaria morbidity were decreasing with increasing treatment coverage even after resistance-related impacts on future morbidity were taken into consideration. Figure 5 displays the difference in costs between strategies A and B. A positive value implies that strategy B is more costly than strategy A. Strategy B was preferred at both very low levels of coverage and high levels of coverage, but strategy A was preferred for coverage fractions ranging from 0.2 to 0.8 for a 20-year policymaking horizon. Broadly speaking, strategy B was the preferred option for a time horizon of five years, while strategy A was preferred if the policymaker's planning horizon extended to 10 or 15 years. For a 40% level of treatment coverage, strategy A resulted in roughly $6 million less in present discounted costs for the 10- and 20-year time horizons, while strategy B resulted in roughly $0.8 million less in present discounted costs over the five-year horizon.

When the cost of ACTs per treatment was increased from $1 to $2 in a sensitivity analysis, the cost of strategy A increased to a greater extent for all levels of treatment coverage (Figure 6). However, the impact on overall cost differences between the two strategies remained unchanged. When the

TABLE 1
Parameter values for simulations*

| Symbol	Description	Value (range for sensitivity analysis)
a	Biting rate (number of bites per female mosquito)	100 per year (50–150)
b_1	Proportion of infectious bites on humans that produce an infection	0.8 (0.4–1.1)
b_2	Proportion of bites by susceptible mosquitoes on infected humans that produce an infection	0.8 (0.4–1.1)
R_0	Reproductive number	100 (50–300)
m	Number of female mosquitoes per human host	Calculated based on R_0 and other parameter values
μ	Mosquito mortality rate	36 per year (24–48)
θ_w	Spontaneous rate of recovery of infected susceptible individuals	0.7/year (0.4–1)
θ_r	Spontaneous rate of recovery of infected resistant individuals	2.4/year (2–3)
α	Excess rate of recovery of treated individuals	12/year (9–15)
τ	Incubation period of parasites in mosquito	10 days (8–12)
γ	Rate of loss of immunity	0.1/year (0.08–0.12)

* Source: See Appendix 4.
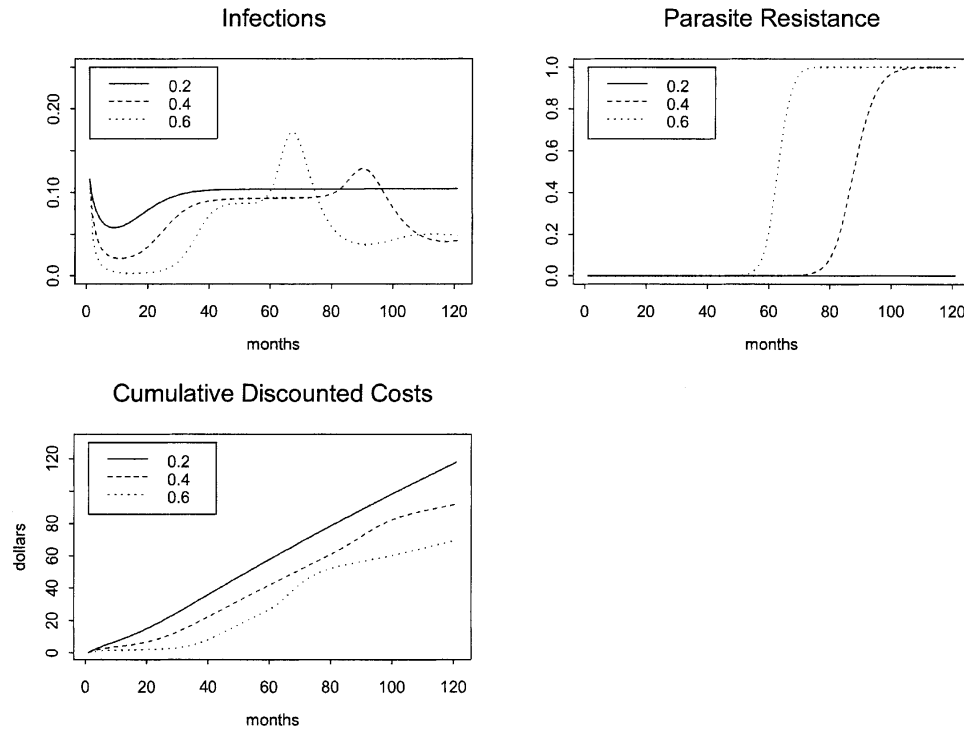
FIGURE 2.   Time path of infections, parasite resistance, and cumulative discounted costs for different levels of treatment coverage.

level of resistance at which a switch from SP to ACT was made in strategy B was changed from 20% in the base case to 60%, the relative advantage of strategy A decreased for coverage less than 0.5 for longer treatment horizons, but increased for coverage greater than 0.5 (Figure 7). In a third sensitivity analysis, the discount rate was increased to 6% from the base case value of 3% (Figure 8). This resulted in an improvement from the base case for shorter time horizons. However, for longer time horizons, the cost advantage of strategy A was smaller relative to the base case. Finally, the value of R_0 was increased from 100 in the base case to 300 to capture settings of more intensive transmission (Figure 9). This variation did not make a significant difference to the relative costs of strategies A and B from the base case.

DISCUSSION

Artemisinin-based combination therapies that combine an artemisinin derivative with another antimalarial such as piperaquine or amodiaquine promise both increased efficacy and a reduction in the rate of development of resistance. Additionally, ACTs may help reduce malaria transmission, which in low transmission settings would reduce the incidence of malaria. The current policy debate centers around whether malaria-endemic countries that face high disease burdens, due in part to increasing CQ resistance, should switch to ACTs, which are much more expensive than current drugs. If these countries were to switch to SP as an interim measure, this would delay the higher treatment cost of ACTs. The downside of the interim measure, however, is that resistance
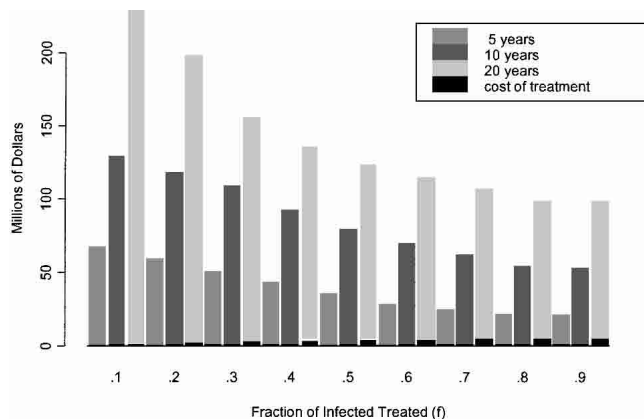

FIGURE 3.   Discounted cost of infection and treatment for strategy A under the base case parameter values.
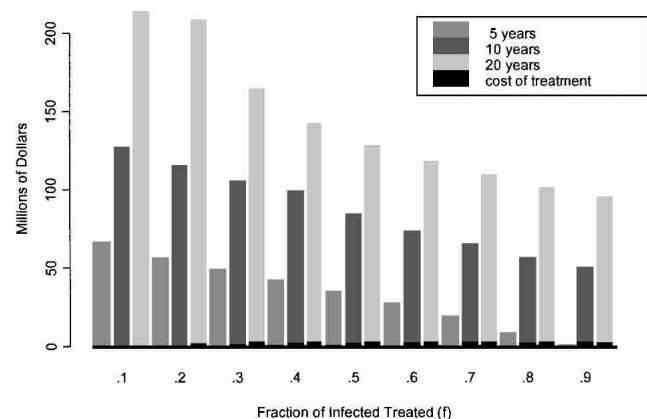

FIGURE 4.   Discounted cost of infection and treatment for strategy B under the base case parameter values.
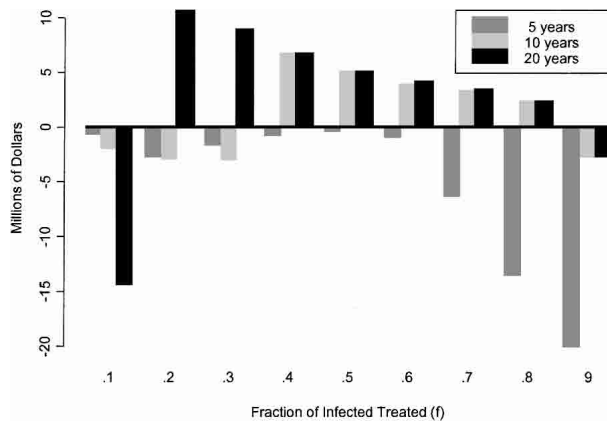
FIGURE 5.   Difference in discounted cost between strategy B and strategy A under the base case parameter values.

FIGURE 7.   Difference in discounted cost between strategy B and strategy A with a switch at a resistance of 60%.

to SP is expected to increase in a few years, leading to increased morbidity and mortality.

Our analysis shows that total discounted costs of infection decrease with increasing levels of coverage with either strategy. This is attributable to faster cure rates, lower morbidity, and consequently to fewer secondary infections. Furthermore, discounted costs of infections decrease more rapidly with treatment coverage for low levels of coverage. After reaching a roughly 50% level of coverage, the decrease in costs is no longer as dramatic, primarily because the increased risk of resistance developing in an area through higher coverage weigh against the benefits of treating more patients.

We find that switching to SP first may be preferable at both very low and very high levels of treatment coverage. At very low levels of treatment coverage and low selection pressure, resistance to SP is not a problem and so the least expensive drug is preferred. At high levels of treatment coverage, resistance evolves so rapidly regardless of which strategy is followed that the faster acquisition of immunity with a less effective drug plays a critical role in determining the superior strategy. We find that for shorter time horizons, it may be economically desirable to switch to SP first to delay the costs of ACTs. If one were only interested in the short term, using the less expensive drug makes better economic sense since the costs of resistance-related morbidity do not enter the policy-
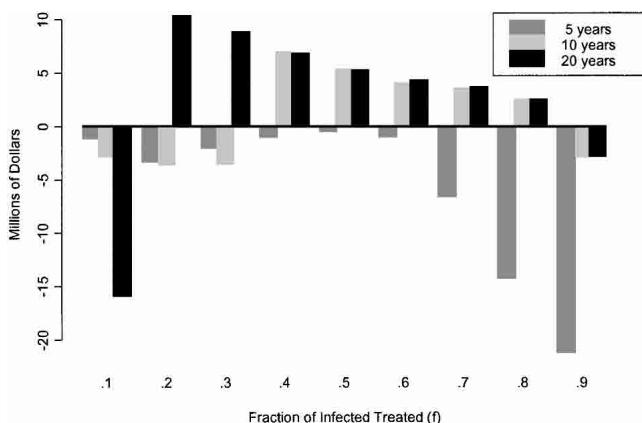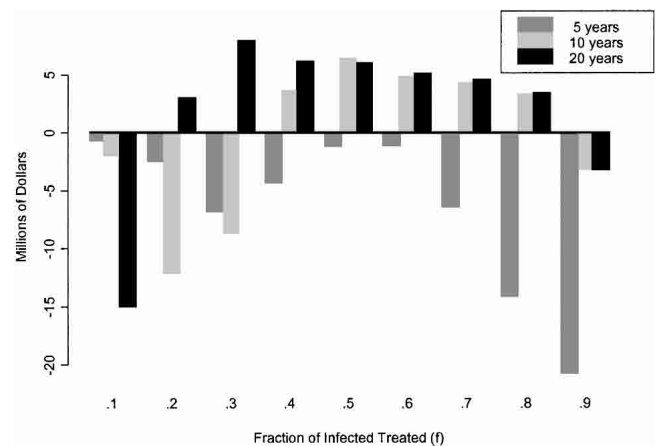
maker's set of considerations. However, for longer planning horizons, a direct switch to ACTs may be desirable given the costs of higher morbidity associated with increasing resistance to SP. With higher intensity of disease transmission, the benefit of switching to ACTs directly is diminished because of greater immunity associated with higher transmission, and thus a lower risk of resistance developing to SP monotherapy. Resistance to SP would be expected to take longer to develop and, therefore, the benefits of switching to SP first increase.

Altering the cutoff level of SP resistance for the change in strategy B from 20% to 60% does not change the difference in costs between the two strategies significantly. Increasing the discount rate places more weight on current costs and benefits compared with those that occur in the future. This reduces the value of introducing ACTs since future resistance-related morbidity costs play a smaller role in the policy decision, making it more desirable to introduce the cheaper drug (SP) initially.

If countries could easily switch between drugs, it would make sense to introduce the cheaper drug (SP) first, and then switch to ACTs before resistance to SP has had much impact on malaria morbidity. However, this is not likely to happen for two reasons. First, malaria-endemic countries have shown

FIGURE 6.   Difference in discounted cost between strategy B and strategy A when the drug 1 treatment cost = 2.
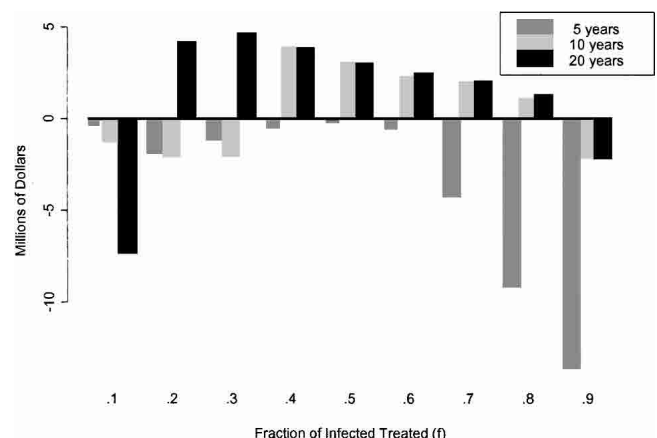

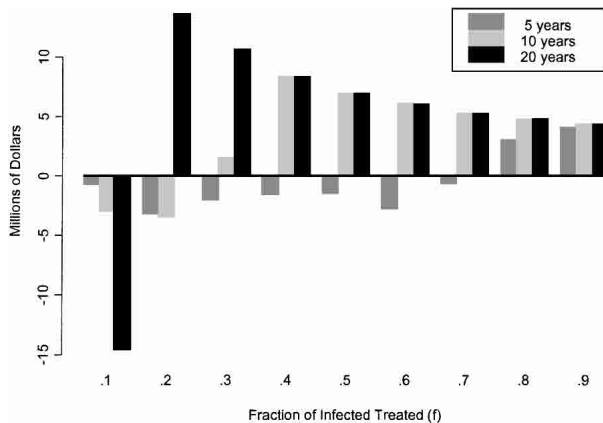FIGURE 8.   Difference in discounted cost between strategy B and strategy A with a discount rate = 6%.

FIGURE 9. Difference in discounted cost between strategy B and strategy A with $R_0 = 300$.

great reluctance to modify their malaria treatment policies proactively in response to impending resistance-related morbidity. The fact that CQ is being used even with high treatment failure rates when an alternative drug (SP) is available is emblematic of policy failures in health decision-making. Second, the costs of each change in treatment policy may be large. These policy change costs are associated with retraining health workers, printing material that explains new dosing regimens, restocking new drugs, and so forth, and can be significant in the short term. In the case of a switch to SP, these policy change costs would have to be amortized over a much shorter life of the drug than in the case of a switch to ACTs. Our analysis, which does not incorporate these policy change costs, therefore errs on the side of being conservative with regard to cost advantages of a direct switch to ACTs.

There are other considerations that play an important role in the selection of the most appropriate antimalarial treatment strategy. First, an important parameter that determines the evolution of resistance to ACTs is the starting frequency of resistance, not just to artemisinin, but also to the partner drug in the combination. With the widespread availability of all antimalarials from private drug sellers in Africa, it may be difficult to control the emergence of resistance to the companion drug, which in turn would expedite the emergence of resistance to the combination. Our model shows that the economic advantages of introducing ACTs immediately are generally lower for higher starting frequencies of resistance to either drug in the combination, although this result depends on the impact of effective treatment on retarding the acquisition of immunity. Second, SP involves a one-day treatment dose, which is much easier to comply with than the five-day treatment of ACTs. To the extent that reduced compliance, which is more likely in the case of ACTs, will significantly expedite the evolution of resistance, our analysis errs on the side of overstating the economic advantages of immediate introduction of ACTs.

Our analysis also indicates that there may be decreasing returns to treatment coverage. In other words, expanding treatment coverage from 10% to 20% may yield much greater benefit than expanding coverage from 60% to 70%. Given the tight constraints placed on malaria treatment resources in sub-Saharan Africa, it may be economically efficient to maximize availability of antimalarials in all areas rather than fo-

cusing resources on just a few areas. However, other factors such as scale economies in treatments may also play a role and work in the opposite direction.

In spite of evidence of significant societal benefits of ACTs, policymakers are likely to be deterred by the immediate cost of ACTs and the burden that adopting a more expensive drug would place on their already overextended health budgets. However, the real choice is not about whether to use ACTs, but whether to introduce them now, or to delay their introduction for a few years while SP could be used. This situation could change with the introduction of new and improved antimalarials, but the prognosis for this happening is bleak. Ultimately, it is the planner's time horizon that will play an important role in naming a successor to chloroquine.

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APPENDIX 1
Derivation of innoculation coefficient

The derivation of the inoculation coefficient is provided by Koella.[9] The inoculation coefficient is given by

$$h = mab_2w \tag{A.1}$$

where m, a, and b_2 are as defined earlier and w is the proportion of mosquitoes with sporozoites in their salivary glands. The population of mosquitoes comprises w, a proportion, v, of mosquitoes that are infected but have not yet developed sporozoites, and uninfected proportion given by $1 - v - w$. The equations of motion for v and w are provided by Koella.[9] If the mosquito population is considered to be at equilibrium, then we can solve for the steady state values of v and w as

$$v = \frac{ab_2e^{-\mu\tau}(e^{-\mu\tau}-1)y}{\mu + ab_1y}$$
$$w = \frac{ab_2e^{-\mu\tau}y}{\mu + ab_1y} \tag{A.2}$$

Substituting back into expression (A.1), we get

$$h = \frac{ma^2b_1b_2e^{-\mu\tau}}{\mu + ab_1y} \tag{A.3}$$

APPENDIX 2
Derivation of the basic reproductive number R_0*

Equations 1–4 can be represented in their most simple form (for the case with no resistance):

$$\dot{x} = \delta - \delta x - hx + \gamma(1 - x - y)$$
$$\dot{y} = hx - (\theta + \delta)y_w \tag{B.1}$$

where $h = \dfrac{Ay}{\mu + ay}$ and $A = ma^2b_1b_2e^{-\mu\tau}$.

Equilibria

$$x(\delta + \gamma) + \frac{xAy}{(\mu + ay)} + \gamma y = \delta + \gamma$$
$$Ax = (\theta + \delta)(\mu + ay) \tag{B.2}$$

We can solve for equilibrium values of $x*$ and $y*$ as $(1, 0)$ and

$$\left[\frac{(\delta + \theta)(a(\gamma + \delta) + (\gamma + \delta + \theta)\mu)}{ab_1(\theta + \delta)(\gamma + \delta) + A(\gamma + \delta + \theta)}, \frac{(\gamma + \delta)(A - (\theta + \delta)\mu)}{ab_1(\theta + \delta)(\gamma + \delta) + A(\gamma + \delta + \theta)}\right]$$

The expression for $y*$ is positive if

$$A - (\theta + \delta)\mu > 0$$
$$\Rightarrow R_0 = \frac{A}{(\theta + \delta)\mu} > 1$$

Stability

An alternative approach is to evaluate the Jacobian matrix

$$J_E = \begin{bmatrix} -\delta - h - \gamma & -x\dfrac{\mu A}{(\mu + Ay)^2} - \gamma \\ h & x\dfrac{\mu A}{(\mu + Ay)^2} - (\theta + \delta) \end{bmatrix} \tag{B.3}$$

at the steady state point, $E = (1, 0)$, which yields

$$J_E = \begin{bmatrix} -\delta - \gamma & -\dfrac{A}{\mu} - \gamma \\ 0 & \dfrac{A}{\mu} - (\theta + \delta) \end{bmatrix} \tag{B.4}$$

For stability, we check that $\det(J_E) < 0$, or equivalently,
$$\left[\frac{A}{\mu} - (\theta + \delta)\right](-\delta - \gamma) < 0.$$

Since $\delta > 0$ and $\gamma > 0$, $\left[\dfrac{A}{\mu} - (\theta + \delta)\right] > 0$, or

$$R_0 = \frac{A}{\mu(\theta + \delta)} > 1.$$

APPENDIX 3
Derivation of f_c

From Equations 2 and 3, we can solve for

$$\frac{h_rx}{y_r} = (\theta_r + \delta) \text{ and } \frac{h_wx}{y_w} = (\theta_w + \delta - \alpha f).$$

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* See page 395 of Anderson and May[8] for a geometric phase plan–based derivation for the basic malaria model.

From our definition of h_w and h_r, we have

$$\frac{h_w}{y_w} = \frac{h_r}{y_r}.$$

Therefore, we can show that

$$f_c = \frac{\theta_r - \theta_w}{\alpha}.$$

APPENDIX 4

Justification of parameter values (see Table 1 for values and range for sensitivity analysis)

Measured values of the Macdonald's stability index (ab_1/μ) vary between 0.5 for *Anopheles gambiae* in Sudan and 4.9 for *An. balabacensis* in Southeast Asia, according to Table 14.6 on page 398 in Anderson and May,[8] which reports values of this index for several regions where malaria is endemic. Our assumed baseline estimate is 6.6 with the index varying between 0.42 and 6.9 in the sensitivity analysis. The specific parameter values are from Koella.[9]

Our baseline level of R_0 is 100. This is a close approximate of the R_0 of 80 recorded by Molineaux and Gramiccia in their work on the Garki Project.[29] The force of infection for a susceptible parasite, h_w, is 0.007 per day for baseline parameter values. This falls in the range of empirically estimated values reported by Anderson and May in Table 14.7 on page 408.[8]

There are no empirical estimates of θ_w or θ_r. Thus, the parameter values used are approximated from those reported by Koella.[9]